Glass Syndrome Unveiled: A Unique Journey through Assisted Reproduction

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Abstract

Glass syndrome (OMIM #612313) is a rare disorder characterized by intellectual disability and distinct facial features, including down-slanting palpebral fissures, crowded teeth, cleft palate, and micrognathia. It was first described by Glass et al. in 1989 in a 16-year-old boy with an abnormal karyotype 46,XY,del(2)(q32.2q33.1) and thereafter found to be caused by disruption of the *SATB2* gene which is encompassed within this cytoregion. We report a 7-year-old Indian girl with Glass syndrome. The patient presented with unclear speech, intellectual disability, restlessness, and stubbornness. Unlike previous cases, she did not exhibit short stature or microcephaly. Her facial dysmorphic features were similar to those in previously reported cases, but she additionally had telecanthus and up-slanting rather than down-slanting palpebral fissures. Notably, this child was conceived through intrauterine insemination (IUI) with donor sperm. Multiplex ligation-dependent probe amplification (MLPA) identified a 2q33.1 deletion, confirmed by real-time polymerase chain reaction (PCR).

Keywords: Glass syndrome; Chromosome 2q32q33 deletion syndrome; *SATB2*-associated syndrome

Introduction

Glass syndrome (OMIM #612313) is marked by intellectual disability and distinct facial features such as down-slanting palpebral fissures, crowded teeth, cleft palate, and micrognathia. The condition arises from a heterozygous deletion in chromosome 2q33.1 or a chromosomal translocation involving 2q33.1 which disrupts the *SATB2* gene, or a heterozygous pathogenic variant in the *SATB2* gene (Zarate et al., 2022). The condition was first described in 1989 in a 16-year-old boy with an abnormal karyotype 46, XY, del (2) (q32.2q33.1) (Glass et al., 1989). We now present a case of Glass syndrome in an Asian Indian girl; this is the first case report of Glass syndrome from India to the best of our knowledge.

Case Presentation

A seven-year-old girl, born after intrauterine insemination (IUI) using donor sperm, presented with unclear speech, intellectual disability, stubbornness, and restlessness. She is in kindergarten, can write the English alphabet and numbers 1-20, but cannot verbalize them. The mother reported motor delay, walking unsupported at 2 years, and bi-syllable words at 9 months, with no further vocabulary development. Primary dentition appeared at 1 year and 3 months. The child had a surgically corrected cleft palate at 1 year and 7 months. She had pneumonia at 3 years, requiring 4 days of hospitalization. She indicated toilet needs by gesturing. The mother's antenatal history was uneventful, and antenatal ultrasounds showed no abnormalities. The girl was born at term via lower segment cesarean section (done in view of a nuchal cord), with a birth weight of 2.3 kg. She was admitted to the neonatal intensive care unit (NICU) for two days due to breathing difficulties and

readmitted at 6 days of life for jaundice and fever and was treated with phototherapy. There is no family history of a similar illness, but the mother was diagnosed to have lung carcinoma.

Figure 1 Images of the patient show a long, triangular face, a prominent beaked nose, up-slanting palpebral fissures, a small mouth, and a pointed chin.

On examination, her height (130 cm, z-score 0.94), weight (20 kg, z-score -1.34), and occipitofrontal circumference (51 cm) were age-appropriate. She exhibited a triangular, long, hypotonic face, telecanthus, up-slanting palpebral fissures, a prominent beaked nose with a wide nasal bridge, a broad nasal tip, a hanging columella, midface hypoplasia, smooth philtrum, repaired cleft palate, dental caries, small uvula, small mouth, hypoplastic mandible, and pointed chin. Arachnodactyly was also noted. Her facial features are shown in **Figure 1**. The rest of the systemic examination was normal.

Blood investigations, including hemoglobin (12.6 g/dL), thyroid-stimulating hormone (1.358 µIU/ml), aspartate transaminase (24 U/L), alkaline phosphatase (301 U/L), calcium (10.01 mg/dL), phosphorus (5.3 mg/dL), and creatinine (0.33 mg/dL), were within normal limits. The electroencephalogram was normal. Ultrasonography of the abdomen and pelvis showed no significant abnormalities.

Informed consent was obtained for genetic testing. Multiplex ligation-dependent probe amplification (MLPA) using SALSA MLPA P245-B1 Microdeletion Syndromes-1A probe mix (MRC-Holland, Amsterdam, Netherlands) revealed a heterozygous deletion of exon 3 of *SATB2* at chromosomal position 2q33.1 (**Figure 2a**). This deletion was validated by real-time polymerase chain reaction (PCR), which showed a relative gene expression reduction (0.6) in the patient compared to the mother (1.2) (**Figure 3**). *ACTB* (beta-actin) served as the housekeeping gene, and reactions were duplicated for real-time PCR. The mother's MLPA was normal (**Figure 2b**). Chromosomal microarray analysis (CMA) (315K and 750K array) did not show any abnormalities. Exon array could not be performed due to financial constraints, and the biological father could not be tested due to confidential paternity.

Discussion

Glass syndrome, also known as chromosome 2q32q33 deletion syndrome or *SATB2*-associated syndrome (SAS) (Zarate et al., 2022), involves a protein that can activate or repress gene expression (Döcker et al., 2014). A gene associated with significantly decreased expression in mutant *SATB2* cases is *UPF3B* (Leoyklang et al., 2013), leading to overlapping clinical features with mental retardation X-linked syndromic 14 (MRXS14) (OMIM #300676) caused by hemizygous variants in *UPF3B*. Common features include a long thin face and long fingers and feet, as observed in our patient. However, speech abnormalities, cleft palate, and behavioral issues pointed more toward Glass syndrome. Unlike previous reports (Glass et al., 1989), our patient did not have short stature or microcephaly. She had similar dysmorphic features except for telecanthus and up-slanting palpebral fissures (Döcker et al., 2014).

The microdeletion detected at chromosome 2q33.1 by the SALSA MLPA probe mix 245-B1 corresponds to exon 3 in the *SATB2* gene [transcript ENST00000417098 (GRCh37)]. This is an intragenic deletion. There is another report of a child conceived by intra-cytoplasmatic sperm injection, diagnosed with SAS due to duplication of the region (Kaiser et al., 2015).

The current management plan includes speech and behavioral therapy, annual ophthalmological examination, and evaluation of nutritional status, growth, and developmental progress at each visit.

This child, conceived via IUI using donor sperm, raises the possibility of ART leading to *SATB2*-related disorders, warranting further research. CMA could not locate the chromosomal coordinates due to low single nucleotide polymorphism (SNP) and copy number variation (CNV) probe density in the deletion region. Karyotyping usually misses microdeletions less

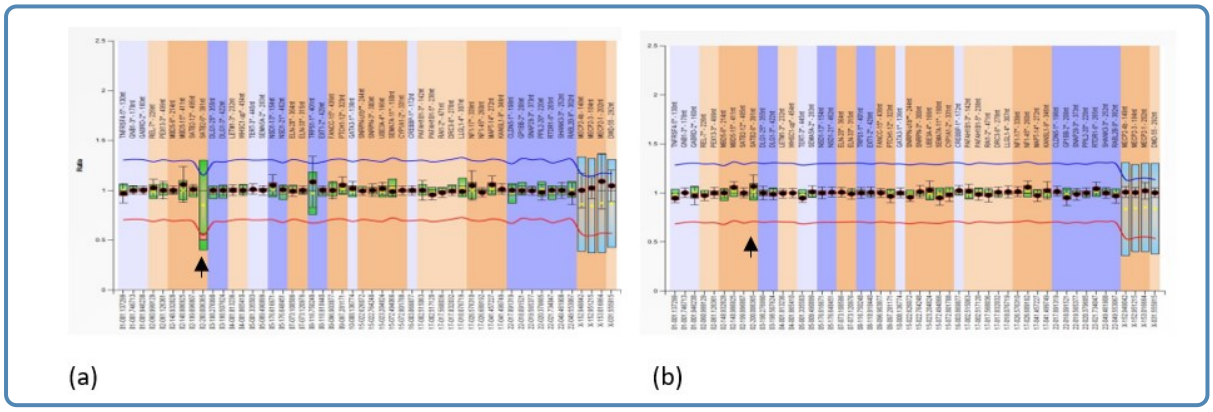

Figure 2 **a**. MLPA ratio chart showing heterozygous 2q33.1 deletion involving exon 3 of the *SATB2* gene in the proband, marked with a black arrow. **b.** Mother's MLPA chart shows normal results.

than 5Mb, making MLPA more useful in such cases. RNA expression studies would help understand the functionality of *SATB2*-associated proteins.

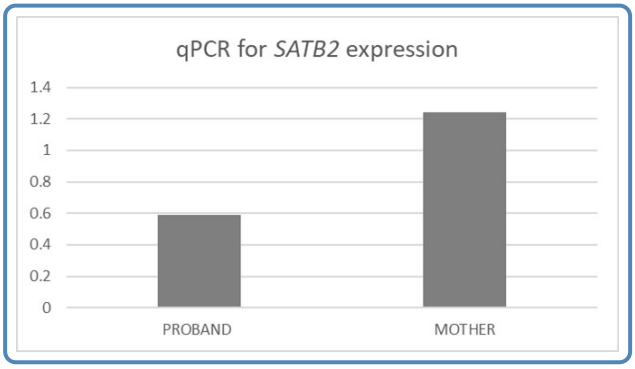

Figure 3 A bar chart representing relative quantification values obtained from real-time PCR in the proband and the mother.

Genetic counseling was challenging as the child was born through assisted reproductive technology (ART) with donor sperm. The father inquired about prenatal detection techniques. Despite improvement after a year of developmental therapy, the diagnosis was hard for the parents to accept. This case highlights the potential of preimplantation genetic testing (PGT) in detecting genetic disorders before ART, although it raises ethical dilemmas and anxiety. PGT can produce complex genetic data, complicating decision-making without a genetic disorder history. Genetic counseling should be recommended before ART, and counselors must disclose that ART outcomes are not always unaffected conceptuses. The mother requires evaluation for lung cancer and is not considering further pregnancies.

Conflict of interests: None

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